IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CHUGAI PHARMACEUTICAL CO., LTD.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 18-1802 (MN)
	)	
ALEXION PHARMACEUTICALS, INC.,	)	
	)	
Defendant.	)	

MEMORANDUM ORDER

At Wilmington this 15th day of April 2020:

As announced at the hearing on April 3, 2020, IT IS HEREBY ORDERED that the disputed claim terms of U.S. Patent Nos. 9,890,377 ("the '377 Patent") and 10,472,623 ("the '623 patent") are construed as follows:

1. "KD for the antigen" shall have its plain and ordinary meaning – "the antibody's KD value for the antigen to which it binds," ('377 Patent, cl. 1, 8, & 9; '623 Patent, cl. 1-5, 9, 10, 13, 14, & 20)[1];

2. "dissociates from the bound antigen under conditions present in an endosome in vivo" needs no construction at this time, ('377 Patent, cl. 1, 8, & 9; '623 Patent, cl. 1-5, 9, 10, 13, 14, & 20);

3. "human IgG or a humanized IgG" means "a human IgG or an IgG antibody having a humanized variable region," ('377 Patent, cl. 1, 8, & 9; '623 Patent, cl. 1-5, 9, 10, 13, 14, & 20); and

4. "the antibody binds to the antigen through the antigen-binding domain of the antibody comprising one or more histidine substitutions at one or more heavy chain or light chain variable region positions and has a KD(pH5.8)/KD(pH7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000" means "the antibody binds to the antigen through the antigen-binding domain of the

[1] The parties only briefed the first three disputed terms – "KD for the antigen," "dissociates from the bound antigen under conditions present in an endosome in vivo," and "human IgG or a humanized IgG" – in relation to their use(s) in the '377 Patent, but agreed that the constructions for those terms "should be the same for both the '377 [P]atent and the '623 [P]atent" and that briefing specific to the '623 Patent was not necessary. (D.I. 74 at 84).

> antibody comprising one or more histidine substitutions at one or more heavy chain or light chain variable region positions, whereby the histidine substitution conveys in part a KD(pH 5.8)/KD(pH 7.4) value of the antibody, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000," ('623 Patent, cl. 9, 10, 13, 14, & 20).

The parties briefed the issues, (*see* D.I. 74), submitted Joint Claim Construction Charts citing intrinsic evidence, (D.I. 41, 63),[2] and a joint appendix (D.I. 75) containing both intrinsic and extrinsic evidence, including expert declarations,[3] and provided tutorials describing the relevant technology, (*see* D.I. 73, 77). The Court carefully reviewed all submissions in connection with the parties' contentions regarding the disputed claim terms, heard oral argument, and applied the below legal standards in reaching its decision.

I. LEGAL STANDARDS

A. Claim Construction

"[T]he ultimate question of the proper construction of the patent [is] a question of law," although subsidiary fact-finding is sometimes necessary. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 135 S. Ct. 831, 837-38 (2015). "[T]he words of a claim are generally given their ordinary and customary meaning [which is] the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (internal

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[2] The parties submitted two Joint Claim Charts – D.I. 41 for the '377 Patent and D.I. 63 for the '623 Patent.

[3] Plaintiff Chugai Pharmaceutical Co., Ltd. ("Plaintiff" or "Chugai") submitted declarations from John C. Williams, Ph.D., a Professor in the Department of Molecular Medicine at the City of Hope, a private, not-for-profit clinical research center, hospital, and graduate medical school with more than twenty years of experience. (D.I. 75 at 484-520, 670-77, 688-95). Defendant Alexion Pharmaceuticals, Inc. ("Defendant" or "Alexion") submitted declarations from Paul W.H.I. Parren, Ph.D., a Professor of Molecular Immunology at the Leiden University Medical Center in Leiden, the Netherlands with twenty-five years of experience. (*Id.* at 521-669, 678-687, 696-780).

citations and quotation marks omitted). Although "the claims themselves provide substantial guidance as to the meaning of particular claim terms," the context of the surrounding words of the claim also must be considered. *Id.* at 1314. "[T]he ordinary meaning of a claim term is its meaning to the ordinary artisan after reading the entire patent." *Id.* at 1321 (internal quotation marks omitted).

The patent specification "is always highly relevant to the claim construction analysis . . . [as] it is the single best guide to the meaning of a disputed term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). It is also possible that "the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. "Even when the specification describes only a single embodiment, [however,] the claims of the patent will not be read restrictively unless the patentee has demonstrated a clear intention to limit the claim scope using words or expressions of manifest exclusion or restriction." *Hill-Rom Servs., Inc. v. Stryker Corp.*, 755 F.3d 1367, 1372 (Fed. Cir. 2014) (internal quotation marks omitted) (quoting *Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 906 (Fed. Cir. 2004)).

In addition to the specification, a court "should also consider the patent's prosecution history, if it is in evidence." *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 980 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). The prosecution history, which is "intrinsic evidence, . . . consists of the complete record of the proceedings before the PTO [Patent and Trademark Office] and includes the prior art cited during the examination of the patent." *Phillips*, 415 F.3d at 1317. "[T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the

invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Id.*

In some cases, courts "will need to look beyond the patent's intrinsic evidence and to consult extrinsic evidence in order to understand, for example, the background science or the meaning of a term in the relevant art during the relevant time period." *Teva*, 135 S. Ct. at 841. Extrinsic evidence "consists of all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Markman*, 52 F.3d at 980. Expert testimony can be useful "to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of skill in the art, or to establish that a particular term in the patent or the prior art has a particular meaning in the pertinent field." *Phillips*, 415 F.3d at 1318. Nonetheless, courts must not lose sight of the fact that "expert reports and testimony [are] generated at the time of and for the purpose of litigation and thus can suffer from bias that is not present in intrinsic evidence." *Id.* Overall, although extrinsic evidence "may be useful to the court," it is "less reliable" than intrinsic evidence, and its consideration "is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence." *Id.* at 1318-19. Where the intrinsic record unambiguously describes the scope of the patented invention, reliance on any extrinsic evidence is improper. *See Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1308 (Fed. Cir. 1999) (citing *Vitronics*, 90 F.3d at 1583).

B. Indefiniteness

"The primary purpose of the definiteness requirement is to ensure that the claims are written in such a way that they give notice to the public of the extent of the legal protection afforded by the patent, so that interested members of the public, *e.g.* competitors of the patent owner, can determine whether or not they infringe." *All Dental Prodx, LLC v. Advantage Dental Prods., Inc.*,

309 F.3d 774, 779-80 (Fed. Cir. 2002) (citing *Warner-Jenkinson Co. v. Hilton-Davis Chem. Co.*, 520 U.S. 17, 28-29 (1997)). Put another way, "[a] patent holder should know what he owns, and the public should know what he does not." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 731 (2002).

A patent claim is indefinite if, "viewed in light of the specification and prosecution history, [it fails to] inform those skilled in the art about the scope of the invention with reasonable certainty." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 910 (2014). A claim may be indefinite if the patent does not convey with reasonable certainty how to measure a claimed feature. *See Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015). But "[i]f such an understanding of how to measure the claimed [feature] was within the scope of knowledge possessed by one of ordinary skill in the art, there is no requirement for the specification to identify a particular measurement technique." *Ethicon Endo–Surgery, Inc. v. Covidien, Inc.*, 796 F.3d 1312, 1319 (Fed. Cir. 2015).

Like claim construction, definiteness is a question of law, but the Court must sometimes render factual findings based on extrinsic evidence to resolve the ultimate issue of definiteness. *See, e.g., Sonix Tech. Co. v. Publications Int'l, Ltd.*, 844 F.3d 1370, 1376 (Fed. Cir. 2017); *see also Teva*, 135 S. Ct. at 842-43. "Any fact critical to a holding on indefiniteness . . . must be proven by the challenger by clear and convincing evidence." *Intel Corp. v. VIA Techs., Inc.*, 319 F.3d 1357, 1366 (Fed. Cir. 2003); *see also Tech. Licensing Corp. v. Videotek, Inc.*, 545 F.3d 1316, 1338 (Fed. Cir. 2008).

II. THE COURT'S RULING

The Court's rulings regarding the disputed claim terms of the '377 and '623 Patents were announced from the bench at the conclusion of the hearing. The Court's rulings are as follows:

> . . . Thank you to everyone and thank you for the arguments. I appreciate your efforts to direct me to the appropriate slides and exhibits to make things easier. At issue in this case, we have two patents[, U.S. Patent Nos. 9,890,377 ("the '377 Patent") and 10,472,623 ("the '623 Patent"),] which share a specification.
>
> There are four terms in dispute. And I am prepared to rule on each of those disputes today. I will not be issuing a written opinion as to those terms, but I will issue an order stating my rulings. I want to emphasize before I announce my decisions that while I am not issuing a written opinion, we have followed a full and thorough process before making the decisions I am about to state. I have reviewed each of the patents, the portions of the prosecution history submitted, as well as the six expert declarations submitted and the other materials included in the joint appendix. There were tutorials submitted by each side, there was full briefing on each of the disputed terms, and there has been argument here today. All of that has been carefully considered.
>
> As an initial matter, I am not going to read into the record my understanding of claim construction law generally or indefiniteness. I have a legal standard section that I have included in earlier opinions, including somewhat recently in *OmegaFlex v. Ward Manufacturing*, C.A. No. 18-1004. I incorporate that law and adopt it into my ruling today and will also set it out in the order that I issue.
>
> As to the person of ordinary skill in the art, the parties have proposed slightly different constructions,[4] but there have not been any arguments suggesting that the differences in their definitions are relevant to the claim construction.

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[4] Plaintiff, through its expert, asserts that "a person of ordinary skill in the field of the inventions [of the patents-in-suit] at the time of the invention would have: 1) a Ph.D. in chemistry, biochemistry, pharmacology, or a related field, with at least four years of experience in biochemical laboratory analysis, including experience with surface plasmon resonance; or 2) an M.D., with at least four years of experience treating blood diseases with antibody therapeutics." (D.I. 75 at 487). Defendant proposes that, "around 2008 to 2009, a person of ordinary skill in the art would have an advanced degree in a relevant field of study, including immunology, biochemistry, molecular biology, or cell biology. . . . The advanced degree would likely be a doctorate level degree (or equivalent degree through training). This person would have additional experience in the research, design, and development of antibodies or characterization of protein-to-protein interaction, in particular antibody-antigen interaction. . . . This experience would encompass 3 to 5 years in an academic research laboratory or in the biotechnology or pharmaceutical industry." (D.I. 74 at 14 (citing its expert's declaration)).

The first term is "KD for the antigen" in claims [1, 8, and 9] of the '377 Patent and some claims of the '623 Patent as well. The parties only briefed this term with reference to the '377 Patent, but agree that the term means the same thing in the two patents at issue. Plaintiff asserts that the term should have its plain and ordinary meaning, which it asserts is "the antibody's KD value for the antigen to which it binds." [(*E.g.*, D.I. 41 at 3).]

Defendant proposes the construction "monovalent equilibrium dissociation constant of an antibody to its antigen." [(*Id.*).]

KD is the dissociation constant, which is a measurement of the propensity of an antibody to separate from its target antigen. The dispute over this term involves Defendant's proposed additions of the words "monovalent" and "equilibrium" to the construction.

Here, I agree with Plaintiff and will give the term its plain and ordinary meaning – "the antibody's KD value for the antigen to which it binds."

This construction is supported by the claim language and the specification of the '377 Patent. The language of claim 1 regarding the term is "providing an antibody that binds to the antigen through the antigen-binding domain of the antibody and has a KD(pH 5.8)/KD(pH 7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 2 to 10,000." The claim thus requires an antibody to bind to an antigen and that "KD" refers to the KD value of the antibody with respect to that antigen.

The specification also supports construing KD as a measure of antigen-binding activity. At column 12, lines 6 through 13, it states: "In the present invention, the difference in the antigen-binding activity between acidic and neutral pHs is not particularly limited as long as the antigen-binding activity at acidic pH is lower than that at neutral pH. However, the value of KD(pH 5.8)/KD(pH 7.4), which is a ratio of dissociation constant (KD) against an antigen at pH 5.8 and that at pH 7.4, is preferably 2 or greater, more preferably 10 or greater, and still more preferably 40 or greater."

The phrase "(KD) against an antigen" in the above passage refers to the KD of the antigen-binding molecule against the antigen to which it binds. [*See also* '377 Patent, col. 13 ll. 4-5 ("When the antigen-binding molecule is an antibody . . . .").]

I decline to read in Defendant's proposed addition of monovalent. The term "monovalent" is not included in the claims and the claims do not limit "KD" to monovalent or divalent binding. The term "monovalent" is mentioned a few times in the specification but so is the term divalent. The specification notes that certain molecules bind monovalently to soluble antigens and divalently to membrane antigens. [*E.g.*, *id.* at col. 67 ll. 22-25; *see also id.* at col. 59 ll. 33-35, col 70 ll. 27-31.]

And the claims include both soluble and membrane-bound antigens. Claim 1 of the '377 Patent, as evidenced by dependent claims 4 and 5, includes both soluble and membrane antigens. Similarly, the independent claims of the '623 Patent include both soluble and membrane antigens, as evidenced by the dependent claims. [*E.g.*, '623 Patent, cl. 2, 10.]

And although the claim uses KD and the specification in places appears to distinguish between KD and apparent KD, in other places [the specification] does not appear to use the word "apparent" [in relation to a dissociation measure] when it otherwise could. For example, in Table 6, discussing membrane-bound antigens, it refers to "little" kd, [*i.e.*, the rate constant of dissociation,] but does not include the word "apparent."

I also decline to read in Defendant's proposed addition of "equilibrium." There does not seem to be a dispute that KD is the equilibrium dissociation constant. And there is no dispute that you don't have to measure it at equilibrium, but can calculate it from other measurements even if equilibrium is not achieved. So with that understanding, I don't think we need to add a word into the construction that is unnecessary and that may add ambiguity.

The second term is "dissociates from the bound antigen under conditions present in an endosome in vivo" also in claims [1, 8, and 9] of the '377 Patent and claims of the '623 Patent. Again, the parties briefed this term with respect to the '377 Patent, but … agree that it means the same [thing] in both patents. Plaintiff again asserts that the term should have its plain and ordinary meaning, which it asserts is "the antibody dissociates from the bound antigen under conditions present in an endosome in vivo, which includes an intraendosomal pH generally in the range of 5.5 to 6.0." [(*E.g.*, D.I. 41 at 3-4).]

Defendant proposes that the term is indefinite or, alternatively, that it means that "at least one antibody of any antigen-

antibody complex taken up by a cell dissociates from the bound antigen under conditions present in the endosome in vivo." [(*Id.*).]

First, as to indefiniteness, for a claim to be held invalid for indefiniteness there must be clear and convincing evidence. [*See Nautilus*, 572 U.S. at 912 n. 10 (citing *Microsoft Corp. v. i4i Ltd. Partnership*, 564 U.S. 91, 95 (2011)).] Here, I have competing declarations and no real cross-examination of the positions; thus, at this time, the Court finds that Defendant has not met its burden to show that this term is indefinite. Should there still be a disagreement regarding definiteness in the future that involves the ambiguity that Defendant asserts exists, Defendant may raise the issue later, if appropriate, after full fact and expert discovery.

As to the proposed constructions, Plaintiff does not dispute that "dissociates" could be met by "at least one antibody," as proposed by Defendant, but says the problem is that one would never know if just one antibody dissociated, and what is relevant is that the antibody has the dissociation constant ratio in the claim.

Here, when I listen to the parties' positions, I am not convinced that there is a real or ripe dispute as to the proposed constructions. If it turns out that a dispute crystallizes such that construction may be appropriate, I will address that after fact and expert discovery.

The third term is "human IgG or a humanized IgG" again in claims [1, 8, and 9] of the '377 Patent and claims of the '623 Patent. Again, the parties . . . agree that it means the same [thing] in both patents. Plaintiff proposes the plain and ordinary meaning, which it states is "a human IgG or an IgG antibody having a humanized variable region." [[(*E.g.*, D.I. 41 at 3).] Defendant proposes "an IgG antibody having a variable region and a constant region, wherein the variable region is human or humanized and the constant region is from a human antibody." [(*Id.*).]

The dispute here is whether the constant region must be from a human antibody. I will construe the term to mean "a human IgG or an IgG antibody having a humanized variable region."

This construction is supported by the specification of the '377 Patent. At column 25, lines 32 through 36, the specification states that '"[h]umanized antibodies', also referred to as reshaped human antibodies, are antibodies in which complimentary determining regions (CDRs) of an antibody derived from a nonhuman mammal, for example, a mouse, are transplanted into the

CDRs of a human antibody." CDRs are part of the variable regions. [(D.I. 74 at 2, 7-8); *see also* '377 Patent, col. 1 ll. 53-56.]

Similarly, the specification also states that "[h]umanized antibodies can be produced by known methods, for example, the CDR of a mouse antibody can be determined, and a DNA encoding an antibody in which the CDR is linked to the framework region (FR) of a human antibody is obtained." ['377 Patent, col. 31 ll. 55-59.]

Again, this passage relies on the features of the variable regions – CDRs and FRs – to explain what makes an antibody humanized and makes no mention of the constant regions.

I decline to read in Alexion's addition that the constant region be from a single human antibody. The specification of the '377 Patent indicates that a constant region from a single human antibody is not necessary and modified constant regions can also be used. For example, at column 32, lines 27 through 31, it states that "[t]he constant regions used for the humanized antibodies of the present invention may be constant regions of antibodies of any isotype. A constant region of human IgG is preferably used, though it is not limited thereto." It then goes on to state[, at lines 35 through 39,] that "[t]he variable and constant regions of chimeric and humanized antibodies of the present invention may be modified by deletion, substitution, insertion, and/or addition, and such, so long as the binding specificity of the original antibodies is exhibited."

I know that Defendant has provided some hypotheticals that it asserts compel me to [further] address the [source of the] constant region. To the extent that issues arise later that relate to the sort hypothesized here, the parties can raise them as appropriate.

And the final disputed term is "the antibody binds to the antigen through the antigen-binding domain of the antibody comprising one or more histidine substitutions at one or more heavy chain or light chain variable region positions and has a KD(pH 5.8)/KD(pH 7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000" in claims 9, 10, 13, 14, and 20 of the '623 Patent.

Plaintiff again proposes the plain and ordinary meaning, which it asserts requires the antibody to have three characteristics. "First, the antibody must bind to the antigen through the antigen-binding domain of the antibody. Second, the antibody must have one or more histidine substitutions in the heavy chain variable region or light chain variable region. Third, the antibody must have

a KD(pH 5.8)/KD(pH 7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000." [(*E.g.*, D.I. 63 at 3-4).]

Defendant, on the other hand, proposes "the antibody binds to the antigen through the antigen-binding domain of the antibody comprising one or more histidine substitutions at one or more heavy chain or light chain variable regions positions in a preexisting antigen-binding domain, whereby the histidine substitution provides the antibody with a KD(pH 5.8)/KD(pH 7.4) value, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen pH 7.4, of 10 to 1,000." [(*Id.*)].

Those are long constructions, but the disputes boil down to whether the histidine substitution or substitutions are into a preexisting variable region sequence and whether it is the histidine substitution(s) that give the antibody the claimed KD ratio.

Here, I construe this term to mean "the antibody binds to the antigen through the antigen-binding domain of the antibody comprising one or more histidine substitutions at one or more heavy chain or light chain variable region positions, whereby the histidine substitution conveys in part a KD(pH 5.8)/KD(pH 7.4) value of the antibody, defined as the ratio of KD for the antigen at pH 5.8 and KD for the antigen at pH 7.4, of 10 to 1,000."

I am not construing this term to require that the histidine substitution occur in a preexisting antigen-binding domain because the specification includes using a variety of antibodies, not simply preexisting ones. [*See e.g.*, '623 Patent, col. 40 l. 60 – col. 41 l. 2.]

As to whether the "histidine substitution provides the antibody" with the claimed ratio of KD values, as proposed by Defendant, as I have already noted, I am going to construe the claim to require "the histidine substitution conveys in part" to the antibody a KD ratio value in the claimed range.

Both parties agree that histidine substitution plays a role in the antibody attaining a KD ratio value in the claimed range, but also that many factors contribute to the KD ratio of an antibody. [(*See* D.I. 74 at 99, 107).] Plaintiff argues, however, that the claims need not be construed to reflect that relationship, while Defendant argues that, notwithstanding its admissions, the histidine substitution must be "responsible" for the antibody achieving a KD ratio value in the claimed range. [(*Id.*).]

First, as to Plaintiff's argument, when a claimed invention has a "fundamental object," the Federal Circuit has instructed that "[t]he claims of the patent must be read in light of the specification's consistent emphasis on [that] fundamental feature of the invention." [*Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1324 (Fed. Cir. 2008), *abrogated on other grounds by Nautilus*, 572 U.S. at 901.]

As Plaintiff acknowledges, "[a]n important additional feature in certain claims of the '623 Patent is the amino acid histidine and its substitution into the variable region of the antibody recited in the claims." [(D.I. 74 at 79).] The invention in the '623 Patent "relates[, *inter alia*,] to methods for improving the pharmacokinetics of antigen-binding molecules and methods for increasing the number of times of antigen binding of antigen-binding molecules, as well as antigen-binding molecules having improved pharmacokinetics, [and] antigen-binding molecules having increased number of times of antigen-binding." ['623 Patent, col. 1 ll. 31-37.] And the patent also repeatedly connects the histidine substitution to those inventive concepts and to increasing the KD(pH 5.8)/KD(pH 7.4) value, [*see, e.g.*, *id.* at col. 5 ll. 26-37, col. 9 ll. 61-66,] which Plaintiff acknowledges is "an important indicator of whether antibody recycling" – i.e., the inventive concepts of the '623 Patent – "would occur[," (D.I. 74 at 5).]

Moreover, the prosecution history supports construing the claim to require that the histidine substitution impacts the KD ratio value. In the March 20, 2019 Amendment and Reply to Office Action of September 20, 2018, during the prosecution of the '623 Patent, the applicant stated[, at page 18]: "In particular, Applicant defined the genus of antibodies by the pharmacological property of having a KD(pH 5.8)/KD(pH 7.4) value of 10 to 1000. By having the recited pharmacological property, conveyed in part by the presence of the additional histidine residue or residues, the antibody is able to bind antigen in [] a pH dependent manner." [(D.I. 75 at 772).]

Defendant's proposal – that the histidine substitution must "provide" the antibody with a KD ratio in the claimed range – to the extent it could require the entirety of the impact [on the KD ratio value] be based on the histidine substitution, is, however, unsupported by the intrinsic evidence. As noted, the prosecution history makes clear that a KD ratio in the claimed range is "conveyed in part" by the histidine substitution, not provided – i.e., conveyed entirely – by the histidine substitution. Moreover, Defendant appeared to agree with this during the argument today and also in the papers, acknowledging that a "plethora of factors

may affect binding affinity, *i.e.*, the KD value of an antibody for an antigen[," (D.I. 74 at 99).] Thus, requiring that the histidine substitution "provide" a KD ratio in the claimed range would improperly narrow the claim by suggesting or requiring that the histidine substitution be the only thing impacting the KD ratio.

Maryellen Noreika

The Honorable Maryellen Noreika
United States District Judge